Selective AV nodal vagal stimulation improves hemodynamics during acute atrial fibrillation in dogs

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Abstract

Wallick, Don W., Youhua Zhang, Tomotsugu Tabata, Shaowei Zhuang, Kent A. Mowrey, Junko Watanabe, Neil L. Greenberg, Richard A. Grimm, and Todor N. Mazgalev. Selective AV nodal vagal stimulation improves hemodynamics during acute atrial fibrillation in dogs. Am J Physiol Heart Circ Physiol 281: H1490–H1497, 2001.—Although the atrioventricular node (AVN) plays a vital role in blocking many of the atrial impulses from reaching the ventricles during atrial fibrillation (AF), a rapid irregular ventricular rate nevertheless persists. The goals of the present study were to explore the feasibility of novel epicardial selective vagal nerve stimulation for slowing of the ventricular rate during AF and to characterize the hemodynamic benefits in vivo. Electrophysiological-echocardiographic experiments were performed on 11 anesthetized open-chest dogs. Hemodynamic measurements were performed during three distinct periods: 1) sinus rate, 2) AF, and 3) AF with vagal nerve stimulation. AF was associated with significant deterioration of all measured parameters (P < 0.025). The vagal nerve stimulation produced slowing of the ventricular rate, significant reversal of the pressure and contractile indexes (P < 0.025), and a sharp reduction in one-half of the abortive ventricular contractions. The present study provides comprehensive evidence that slowing of the ventricular rate during AF by selective ganglionic stimulation of the vagal nerves that innervate the AVN successfully improved the hemodynamic responses.

Atrial fibrillation (AF) has been long recognized as one of the most frequent chronic arrhythmias. Although the restoration and maintenance of normal sinus rhythm is the ultimate goal, it is frequently unachievable. Therefore, ventricular rate (VR) control during AF remains the only realistic long-term solution in a majority of patients (15). Normally, the atrioventricular node (AVN) plays a vital role in blocking many of the rapid atrial impulses from reaching the ventricles. However, this filtering property of the AVN is insufficient to prevent a rapid irregular VR from being elicited during AF. Although drugs are generally used to depress the AVN conduction and thus to control the VR, the use of drug therapy for this purpose is limited by the lack of efficacy in some patients and intolerability due to side effects in others (7, 15). Recently, slow pathway modification via discrete lesions in the posterior approaches has been developed to achieve slower VR while preserving the AVN. This technique showed some encouraging clinical results in drug refractory AF patients, but with inconsistent success rates (15–76%) among different investigators and with recurrence of rapid VR in up to 25% of cases (10, 21).

The conduction through the AVN is normally altered by changes in the autonomic control of the heart (32). Many investigators (2, 5, 6, 11, 12, 14, 17, 23–26) have shown that stimulation of parasympathetic nerves, which selectively innervate the AVN, further delays activation of these parasympathetic nerves via endocardial nerve stimulation in rabbits. Similarly, activation of these parasympathetic nerves via endocardial stimulation has resulted in slowing of VR during AF in dogs (28). However, these studies did not evaluate the hemodynamic consequences of vagally induced ventricular slowing. Furthermore, the anatomic basis of the epicardial approach for selective parasympathetic stimulation has been well established in animal models, and also has been reported in humans (5). Therefore, the goals of the present study were to expand the currently available information by exploring the feasibility of epicardial selective nerve stimulation for slowing of the VR during AF, and by characterizing the hemodynamic benefits of vagally slowed VR in vivo.

METHODS

The experimental protocol was approved by the Animal Research Committee of the Cleveland Clinic Foundation. All experimental procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Surgical preparation. Eleven adult mongrel dogs (23–30 kg body wt) were premedicated with thiopental sodium (20 mg/kg) intravenously and intubated and ventilated with
room external jugular vein was cannulated to infuse
normal saline solution at 100–200 ml/h to replace sponta-
neous fluid losses. Standard surface electrocardiogram (ECG)
leads (I, II, and III) were monitored continuously throughout
the entire study. Intermittent arterial blood gas measure-
ments were taken and ventilator adjustments were made to
correct any metabolic abnormalities. A rectal probe was used
to monitor rectal temperature. An electrical heating pad was
dthen placed under the animal and operating-room lamps
were used to maintain a body temperature of 36–37°C.

The right femoral artery was cannulated and a microm-
rometer-tipped catheter pressure transducer (Millar; Hous-
ton, TX) was inserted and advanced into the thoracic aorta
ear the aortic valve to monitor systemic blood pressure.
Another Millar catheter was inserted through left carotid
ery and advanced so that the tip was in the left ventricle
(LV) to record LV pressure. Before being inserted, both cath-
ters were soaked in warm saline solution for 30 min and
preciobated. After a median sternotomy was performed, a
percardium cradle was created to support the heart. Cus-
tom-made Ag-AgCl quadripolar plate electrodes were su-
tered to the high right atrium and right ventricular apex for
bipolar pacing and recording (Fig. 1). Similar bipolar plate
 electrodes were also sutured to two epicardial fat pads (Fig.
1) that contain parasympathetic neural pathways selectively
innervating the sinus node (SN) and the AVN, respectively
(24). The SN fat pad was located at the right pulmonary vein
atrial junction. The AVN fat pad was located at the junction
of inferior vena cava and the left atrium. The ascending aorta
was isolated and a flow-probe (16 or 20 A) was placed around
it and connected to a flowmeter (model HT 207, Transonic
System; Ithaca, NY) to measure aortic blood flow. All signals
(surface ECGs, right atrial and ventricular electrograms,
arterial blood pressure, LV pressure, and aortic flow) were
amplified, filtered, digitized, and continuously displayed on a
monitoring system (Prucka Engineering). In addition, these
signals along with calibration signals were simultaneously
recorded on magnetic tape (model 4000A, Vetter Digital) for
later computer analysis with the use of an Axoscope (Axon
Instruments) and custom software programs.

Electrical stimulation. A programmable eight-channel
stimulator (Master-8, AMPI) was used to generate the de-
sired sequence of rectangular impulses for atrial pacing or
nerve stimulation. The amplitude of the impulses (in mA)
was determined by current isolators (model A360, WPI) that
also permitted alternation of the polarity of the impulse to
reduce the effects of polarization at the electrode-tissue in-

Study protocol. After the surgical procedures were com-
pleted, each study consisted of three periods. First, a stabi-
ized sinus rhythm was slowed by SN fat-pad stimulation (4–7 mA,
50–mu pulse duration at 20 Hz), which provided selective vagal stimulation
before all baseline hemodynamic values (surface ECG, right
atrial and ventricular epicardial ECGs, aortic pressure, LV
pressure, and aortic flow) were collected. During this period,
the R-R intervals were automatically measured online by a
computer and the average (±SD) of 100 consecutive sinus
intervals was determined. Second, AF was induced by a
one-step maneuver. AF was initiated by brief burst (5–10 s)
of right atrial pacing (5–10 mA, 1-ms pulses at 20 Hz) and
maintained by SN fat-pad stimulation (4–7 mA, 50-μs pulse
duration at 20 Hz), which provided selective vagal stimulation
to the SA node and surrounding atrium. Note that SN
fat-pad stimulation did not capture the atrium. In this fash-
ion, AF could be maintained for many hours and in some
cases spontaneous AF persisted even when the supporting
vagal stimulation was withdrawn. After a period of AF sta-
bilization of at least 15 min, a new set of electrical and
hemodynamic recordings was made. Third, while still main-
taining the AF, the VR was slowed by AVN fat-pad stimula-
tion. Although such stimulation can affect both pre- and
postganglionic structures, it is assumed that the former have
a lower threshold of activation (3, 18). Because the neuro-
transmitter release resulting from this pre- and postgang-
lionic vagal stimulation (VS) is mainly limited to the AVN
region, the abbreviation AVN-VS will be used to describe this
modality. AVN-VS was started at a low stimulator output of
<3 mA at 20 Hz and 50 μs pulse duration. Because hemody-
namics are dependent on heart rate during AF and because it
is presumed that they are best at a rate close to the sinus rate
(19), the amperage of stimulation was adjusted until the
average heart rate response was slowed to the previously
determined sinus rate. Notably, due to the very short dura-
tion of the nerve pulses and their relatively low intensity, the
AVN-VS never resulted in capturing of the nearby ventricu-
lar myocardium. The term “subthreshold” used in the text is
therefore applied to indicate that the nerve stimulation was
not accompanied by direct ventricular pacing. After stabil-
ilization of the slowed rate (10–15 min), a third set of electrical
and hemodynamic data was collected (AF + AVN-VS).

Data acquisition and analysis. The tape-recorded data
were played back off line and digitized at a rate of 1 kHz-
per-channel by Axoscope (Axon Instruments). The R-inte-
vals, systolic and diastolic aortic blood pressures, peak LV
systolic pressure (LVSP), end-diastolic pressure (LVEDP),
and stroke volumes (SV) were measured beat by beat by a
custom-made software for each period of recording. The LV
first time derivative of LV pressure (dP/dt) was derived from

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**Fig. 1.** Illustration shows a posterior view of the heart and positions of the epicardial fat pads described in the text. ● Bipolar stimulating electrodes; SVC, superior vena cava; HRA, high right atrium; PA, pulmonary arteries; Ao, aorta; RPV, right pulmonary veins; LPV, left pulmonary veins; SN, sinus node; AVN, atrioventricular node; IVC, inferior vena cava; RV, right ventricle; LV, left ventricle.
LV signal. To determine the SV (in ml), the aortic flow signal from the probe (in l/min) was time integrated for the duration of each cardiac cycle (in ms). Cardiac output was then calculated as a product of the average SV and heart rate. The SV and the cardiac output determined in this fashion represented the total LV outflow minus coronary flow. All hemodynamic measurements were averaged for at least 100 ventricular cardiac cycles after stable average heart rate had been achieved. Preliminary experiments showed that samples with such duration permit correct evaluation of the measured parameters. The number of “abortive beats” was also determined in each step of the protocol. These were beats for which ventricular depolarization occurred, but the subsequent contraction was insufficient to open the valve and produce aortic flow. Naturally, such beats were associated with short ventricular coupling intervals, such as those present during AF. A given beat was classified as abortive if the corresponding SV was < 1 ml.

Echocardiographic measurements. Epicardial echocardiography was performed using commercially available equipment (Sequoia model C512, Acuson; Mountain View, CA) with a 3.5-MHz phased-array transducer. The LV end-diastolic (EDV) and end-systolic (ESV) volumes were measured by single plain Simpson’s rule (9). From the volumes obtained, LV ejection fraction (EF) was calculated as EF = (EDV – ESV)/EDV × 100 (%).

Statistical analysis. Data are expressed as means ± SD. Hemodynamic differences during sinus rhythm, AF, and AF + AVN-VS were evaluated with an analysis of variance (ANOVA). If the ANOVA revealed significance, it was followed by multiple comparisons with Bonferroni correction. Abortive beats during the AF and AF + AVN-VS periods were compared using a paired Student’s t-test. For single comparison, a value of P < 0.05 was required for statistical significance.

RESULTS

Neural effects of epicardial stimulation of fat pads. Figure 2 illustrates that during sinus rhythm (cycle length of 490 ms and AVN conduction time of 150 ms; Fig. 2A), stimulation of the SN fat pad produced strong chronotropic effect (cycle length of 1,180 ms; Fig. 2B) that was associated with a shortening of the AVN conduction time (130 vs. 150 ms). The dromotropic effect of this vagal stimulation was complex. It depended on such indirect factors as the prolongation of the cycle length and a possible shift of the sinus pacemaker (30). A direct effect via nerve fibers innervating the AVN and affected by the SN fat-pad stimulation could not be ruled out. Previous reports (see, e.g., Ref. 23) described such anatomic aberration, when preganglionic parasympathetic nerve projections to the AVN pass in close proximity to the right pulmonary vein fat pad. Pacing the atria at a constant cycle length tested the direct effect of the SN fat pad. It was found to be present in 2 of 11 animals (see Induction and maintenance of AF).

In contrast, subthreshold AVN-VS did not affect the sinus rate, even when the intensity was high enough to produce strong depression of AVN conduction. In this example (Fig. 2C), 2:1 ratio of Wenckebach blocks and a substantial delay (194 vs. 150 ms) of the conducted beats were observed, whereas the sinus cycle length remained unaffected. Thus, based on the functional outcome, the effects of the SN fat pad maneuver were mostly limited to the SN and its surrounding atrial tissues, whereas the AVN-VS affected the nodal conduction (2, 26).

Induction and maintenance of AF. AF was inducible in all 11 dogs by rapid right atrial pacing. Although continuous rapid right atrial pacing could be used to maintain AF over a prolonged period of time, large pacing artifacts were frequently present in some electrical signals. Subthreshold stimulation of the SN fat pad, presumably by shortening the refractoriness of the atrial tissues surrounding the SA node and by increasing the overall dispersion (6, 33), successfully maintained AF in 8 of 11 dogs while permitting “clean” recording traces (Fig. 2D). In two of the eight dogs, stimulation of the SN fat pad, while successfully maintaining the AF, also affected the AVN and thus the VR.

Fig. 2. Effects of subthreshold epicardial stimulation of the fat pads. A: control sinus rate. Numbers refer to the sinus cycle length and the AV conduction time, respectively. B: stimulation of the SN fat pad. Note the strong chronotropic effect and the associated shortening of the control AV conduction time. C: stimulation of the AVN fat pad. There was no change in the control sinus cycle length, whereas AV conduction was strongly depressed and 2:1 Wenckebach periodicity was observed. D: atrial fibrillation (AF) alone (left), followed by AF in combination with AVN fat-pad stimulation (right). Note the slowing of the ventricular rate during vagal stimulation. ECG, electrocardiogram; RA, right atrium; VS, vagal stimulation.
Finally, in the remaining three dogs, the SN fat-pad stimulation required suprathreshold amplitudes resulting in atrial capture. Therefore, in the latter five animals, AF was maintained by high-rate right atrial pacing.

Selective AVN-VS during AF. Notably, AVN-VS had no apparent effect on the ongoing AF. That is, both the frequency and waveforms of atrial electrograms during AF did not appear to change when AVN-VS was applied. However, the reduction of VR started immediately (within seconds) after AVN-VS was initiated (Fig. 2D) and terminated abruptly after its cessation. The magnitude of these responses was dependent on the stimulation intensity and varied among animals. The average AVN-VS amplitude was adjusted to bring the heart rate to the sinus rate level, that is, the average amperage was 6.3 ± 2.4 mA (range 1.5 to 10 mA). Because the pulses were very short (50 μs), neither the atria nor the ventricles were excited even at the highest amperage levels used.

Hemodynamic measurements during sinus rhythm, AF, and AF + AVN-VS. Figure 3 shows the changes in consecutive R-R intervals observed in one of our experiments during the three periods of the study protocol. The left 100 cardiac cycles were recorded during sinus rhythm at regular R-R intervals of 460 ms (130 beats/min). AF resulted in rapid and irregular ventricular responses compared with that found during sinus rhythm (the middle 200 beats). That is, the average R-R interval was 250 ms (240 beats/min). Local stimulation of the AVN fat pad (selective parasympathetic ganglionic stimulation to AVN) prolonged the R-R intervals to an average of 465 ms, a VR of 129 beats/min (the selection of the right 200 beats). With this increased average R-R interval, there was a corresponding increase in its variation during the VS.

Figure 4A shows the hemodynamic signals during normal sinus rhythm in a representative experiment. Note the consistent activation of the heart from the atria and the subsequent ventricular activation. The significantly shortened average R-R intervals during AF were accompanied with worsening of the hemodynamics (Fig. 4B). Notably, rapid irregular electrical activation of the ventricles during AF resulted in many abortive LV contractions in this study (see asterisk in Fig. 4). As previously explained, abortive LV contraction was associated with electrical activation of the ventricle but the resultant peak systolic LVP was far below the diastolic aortic blood pressure level (Fig. 4B, inset). Thus the aortic valve did not open and no blood was ejected from the LV. In this study, the beat was considered to be abortive when the electrical activation was followed by an ejection of <1 ml of blood.

With the stimulation of the parasympathetic nerves to the AV node, there was a dramatic reduction of the number of abortive LV contractions along with an improvement of the remaining hemodynamic responses (Fig. 4C).

Composite hemodynamic responses. The hemodynamic responses in 11 experiments during sinus rhythm, AF, and AF + AVN-VS are summarized in Table 1. In addition to the average R-R interval, the variability of consecutive cardiac cycles was evaluated in each animal. Thus, the R-R interval variability measured on beat-by-beat basis during sinus rate was only 0.28% of the average cardiac cycle, whereas during AF it increased to 15.93% (compare with Fig. 3). During AF + AVN-VS there was a prolongation of the average R-R interval (Table 1, 485 ms) along with an increased beat-by-beat variability of 26.64%.

In general, the induction of AF resulted in rapid irregular R-R intervals that led to a reduced peak LVSP, whereas the LVEDP increased. The depression of LV function during AF was also indicated by both +LV dP/dt and −LV dP/dt. Furthermore, the increased rate was accompanied by high presence of abortive beats during AF (41%), resulting in reduction of the average stroke volume compared with sinus rhythm (17.7–8.9 ml, P < 0.025). Despite the increased VR, this marked reduction in stroke volume led to a significant reduction in cardiac output (2.2–1.7 l/min, P < 0.025).

These reductions in LV function during AF (compare hemodynamic measurements in middle vs. left columns in Table 1) were substantially reversed by concurrent application of local VS to the AVN (compare Fig. 3. Rhythm dynamics observed during the 3 stages of the experimental protocol. The first 100 consecutive R-R intervals were recorded during sinus rate, the next 200 intervals represent beats recorded during the period of AF, and the final 200 intervals are from consecutive beats recorded during AF accompanied by AVN-VS. See the text for details.
Fig. 4. A: typical electrical and hemodynamic signals recorded and measured in this study. These traces have been recorded during normal sinus rate. B: electrical and hemodynamic changes observed during AF. C: changes after application of AVN-VS. Inset: Ao pressure (AoP) and LV pressure (LVP; in mmHg) signals on same vertical scale and illustrates the absence of aortic flow (AoF; in l/min) when LVP < AoP, resulting in “abortive” beats (*). dP/dt, first time derivative of LVP (in mmHg/s). Note that B and C have a common horizontal scale.

Table 1. Hemodynamic responses during sinus rhythm, AF, and AF + AVN-VS with VR slowing to 100% of the sinus cycle length

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sinus Rhythm</th>
<th>AF</th>
<th>AF + AVN-VS</th>
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<tbody>
<tr>
<td>R-R interval, ms</td>
<td>481 ± 52</td>
<td>311 ± 53†</td>
<td>485 ± 76*</td>
</tr>
<tr>
<td>Longest observed R-R interval, ms</td>
<td>483 ± 52</td>
<td>485 ± 101</td>
<td>831 ± 174</td>
</tr>
<tr>
<td>Shortest observed R-R interval</td>
<td>478 ± 53</td>
<td>249 ± 35</td>
<td>278 ± 38</td>
</tr>
<tr>
<td>R-R variability, % of R-R</td>
<td>0.3 ± 0.2</td>
<td>16 ± 9</td>
<td>27 ± 6</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>105 ± 18</td>
<td>84 ± 15†</td>
<td>96 ± 19*</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>79 ± 18</td>
<td>67 ± 13†</td>
<td>71 ± 18</td>
</tr>
<tr>
<td>LVSP, mmHg</td>
<td>105 ± 15</td>
<td>69 ± 7†</td>
<td>86 ± 11*</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>5.7 ± 3.6</td>
<td>9.7 ± 4.7†</td>
<td>9.5 ± 4.4</td>
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<tr>
<td>+LV dP/dt, mmHg/s</td>
<td>2.029 ± 534</td>
<td>1,668 ± 379†</td>
<td>1,862 ± 477*</td>
</tr>
<tr>
<td>−LV dP/dt, mmHg/s</td>
<td>−2.335 ± 908</td>
<td>−1,230 ± 528†</td>
<td>−1,660 ± 651*</td>
</tr>
<tr>
<td>SV, ml/beat</td>
<td>17.7 ± 4.1</td>
<td>8.9 ± 3.0†</td>
<td>15.5 ± 4.6*</td>
</tr>
<tr>
<td>Abortive beats, %</td>
<td>0</td>
<td>41 ± 15†</td>
<td>21 ± 11*</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>2.2 ± 0.5</td>
<td>1.7 ± 0.4†</td>
<td>1.9 ± 0.4</td>
</tr>
</tbody>
</table>

Values are means ± SD for 11 dogs. AF, atrial fibrillation; AVN, atrioventricular node; VR, ventricular rate; VS, vagal stimulation; LV, left ventricle; SBP, systolic blood pressure; DBP, diastolic blood pressure; SP, systolic pressure; EDP, end-diastolic pressure, dP/dt, first time derivative of pressure; SV, stroke volume; CO, cardiac output. Each parameter was determined from a sample of 100 consecutive ventricular cycles in each dog. *P < 0.025, comparison vs. AF. †P < 0.025, comparison vs. sinus rhythm.
hemodynamic measurements in right vs. middle columns in Table 1). In particular, whereas the systolic and diastolic aortic blood pressures significantly decreased as the result of depressed ventricular function during AF, the localized AVN-VS reversed these trends of both aortic pressures back toward the values observed during sinus rate. Similarly, significant improvements were documented in LVSP, $\pm$LV dP/dt, and SV ($P < 0.025$). The cardiac output was increased and the LVEDP decreased even though the trend did not reach statistical significance.

**Echocardiographic results.** Successful echo evaluations were performed in parallel with the electrophysiological protocol in five of these acute experiments (Table 2). The LV EF significantly decreased during AF ($P < 0.025$) along with the significant decrease in the LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) ($P < 0.025$) compared with those at the baseline sinus rhythm. Note that despite the decrease in the LVEDV, the corresponding LVEDP (Table 1) was increased, suggesting decreased LV compliance. During AVN-VS, LV EF increased significantly ($P < 0.025$) along with the significant increase in the LVEDV and LVESV ($P < 0.025$), compared with AF alone.

**DISCUSSION**

**Major findings.** The first major finding of this study is that one can rapidly and reversibly control VR during AF via a selective stimulation of the epicardial parasympathetic nerves that project to the AVN. Second, with this mode of controlling of VR, an improvement in hemodynamics is achieved, although a complete return to normal values (as in sinus rate) was not obtained. Third, in this study, we demonstrated that VS through right pulmonary vein fat pad could maintain AF once it was induced. This mode of stimulation could be served as an animal model of vagal facilitation of AF.

In summary, the induction of AF resulted in rapid irregular R-R intervals and the high presence of abortive beats during AF, which resulted in an average reduction of the stroke volume compared with sinus rhythm. Despite the increased VR during AF, there was a significant reduction in cardiac output. The reduction in myocardial performance led to reduced peak LVSP, $+$LV dP/dt, and $-$LV dP/dt, whereas LVEDP increased. The LV EF significantly decreased during AF along with the significant decrease in the LVEDV and LVESV compared with those at the baseline sinus rate.

The present study provides evidence that selective epicardial AVN VS improves hemodynamics during AF. That is, significant improvements were documented in LVSP, $\pm$LV dP/dt, and SV. LV EF was increased significantly along with the LVEDV and LVESV compared with AF when the vagal stimulation to the AVN was applied.

The presence of atrial synchronized contractions, which could contribute to the ventricular filling, was lacking during both AF alone and AF with concomitant AVN-VS. However, the slowing of VR by VS increased the LV volume and thus the preload of the heart (Table 2). This could be one of the major factors in improving the hemodynamic responses observed in the present study.

**AVN nerve stimulation as an alternative tool for VR control during AF.** The failure of consistent anatomic modification of the AVN via limited ablation lesions leaves complete nodal destruction as the remaining alternative therapy. This makes the patient permanently dependent on the pacemaker to provide adequate VR control after an irreversible total ablation of the AVN. Moreover, the pacing produces an undesirable alteration of the normal sequence of ventricular depolarization. It would be preferable to achieve VR slowing during AF without inflicting a permanent damage to the AVN, thus preserving also the anterograde ventricular activation. Because of the limitations and drawbacks of the current available treatments, new treatment options such as the one tested in this study deserve attention.

Because AVN plays a vital role in blocking many of the atrial impulses and subsequently slowing VR in AF, one attractive idea is to take advantage of the rich supply of vagal nerves to the nodal region. If these nerves can be selectively stimulated, then a majority of atrial impulses would be blocked within the AVN and slowing the VR to a more tolerable level would be achieved. Mazgalev et al. (20) demonstrated this principle and elucidated the mechanism of parasympathetic modification of the AVN during AF in vitro. These rabbit heart studies were designed to test the theoretical hypothesis that vagally induced slowing of the VR during AF is feasible. We were able to show that brief bursts of subthreshold (for the myocardium) postganglionic VS produced hyperpolarization of the AVN fibers that led to depressed conduction and a substantial prolongation of the ventricular (R-R or His-to-His) intervals during simulated AF. These effects were dependent on the intensity of the postganglionic VS and the frequency of its application, although the amplitude of the stimulation current remained below the threshold of excitation of the cardiac tissue. It should be noted that vagal modulation of the AVN conduction during AF might also involve alterations in the atrio-nodal engagement, although direct evidence for vagally induced effects on the inputs to the AVN during AF is not available.

<table>
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<th>Table 2. Echocardiographic evaluations during sinus rhythm, AF, and AF $+$ AVN-VS with VR slowing to 100% of the sinus cycle length</th>
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<tr>
<td>Sinus Rhythm</td>
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<tr>
<td>LV-EDV, ml</td>
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<tr>
<td>LV-ESV, ml</td>
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<td>LV-EP, %</td>
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</table>

Values are means $\pm$ SD; $n = 5$ dogs. EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume. $^*P < 0.025$, changes vs. AF; $^\dagger P < 0.025$, changes vs. sinus rhythm.
**Historical perspective.** For more than 100 years, scientists have stimulated the peripheral cervical vagi (preganglionic parasympathetic nerve fibers) that innervate the heart. This stimulation results in overall negative chronotropic, dromotropic, and inotropic responses. The cell bodies of the postganglionic parasympathetic nerve fibers, which selectively innervate limited nodal regions or the ventricles of the heart, have been identified for both animals and humans (2, 5, 6, 8, 11–14, 17, 23–26).

Mazgalev et al. (20) found that vagally induced slowing of the VR during AF is feasible via endocardial nerve stimulation. Recent in vivo experiments (28, 29) utilized an endocardial approach (superior vena cava, coronary sinus, or the right pulmonary artery) and demonstrated vagally mediated slowing of VR during AF. Ali et al. (1) reported that stimulating the right atrial ventral ganglionated plexus in dogs resulted in slowing of VR during supraventricular tachycardia, along with an improvement in arterial and LV pressures. In this study, the nerve stimulation affected the sinus nodal and possibly other regions of the heart besides the AVN (22). Until now, no complete study of the systemic hemodynamic effects produced by selective AVN parasympathetic stimulation during AF has been reported.

**Study limitations.** First, certain limitations are imposed by the design of these acute open-chest experiments that required anesthesia and maintenance of AF by SN fat-pad stimulation. Furthermore, whether the selective AVN vagal stimulation has a prolonged effect on the hemodynamics during AF needs evaluation. Some studies (27) have reported the so-called “fading effect.” The latter refers to the gradual reduction in the degree of heart rate slowing that is typically observed in vitro experiments. The underlying mechanism could be the limited supply of choline in vitro that is needed for acetylcholine synthesis (4, 31). Indeed, a report by Schauerte et al. (28) suggested stable ventricular slowing in an open-chest dog model over a period of 20 h. Nevertheless, chronic studies are needed to evaluate the effects of AVN-VS in conscious subjects under conditions of spontaneous AF, normal basic autonomic tone, and during exercise.

Second, the present study used an epicardial approach as opposed to an endocardial approach to selectively stimulate the parasympathetic nerves that innervate the AVN. At this point, it is difficult to predict which approach may be preferable. A major advantage of the former is the lower required intensity, probably due to delivery of stimulation directly at the nerve fibers. Low intensity has the benefit of prolonging the life of potential implantable devices. More importantly, it may reduce the risk of side effects such as discomfort and/or pain. With a typical impedance of 1,000 Ω, the AVN-VS impulses in our experiments were ~5 V, which is several times less than when the endocardial basket electrode was used (28). Multiple-pole catheter stimulation has been applied to conscious human subjects in an electrophysiological catheterization laboratory but the practice was abandoned because these patients expressed discomfort (A. L. Waldo, personal communication). Conscious experiments are needed to evaluate the risks of concomitant afferent nerve stimulation that could evoke pain.

Third, further efforts are needed to establish the mechanisms underlying the variability of the R-R intervals observed in this study and to determine ways for regularization of the rhythm. It would be desirable to explore the feasibility for a controlled beat-to-beat delivery of VS to achieve a predetermined VR slowing and avoid excessively long R-R intervals.

Currently, one might assume that the epicardial approach would require extensive open-chest surgery and could only be justifiably applied in some postoperative patients with AF. However, with the development of new technologies, it may become a viable option. For example, a transcutaneous approach for epicardial ablations is presently being used and may provide the means for selective epicardial nerve stimulation (16).

In conclusion, the present study provides comprehensive evidence that slowing of the VR during AF by selective epicardial ganglionic stimulation of the vagal nerves innervating the AVN successfully improved the hemodynamic responses. Further studies are needed to elucidate the optimal parameters for delivery of this new modality and to evaluate its long-term effects.

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